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Invited review

The need for new approaches in CNS drug discovery: Why drugs have failed, and what can be done to improve outcomes

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ABSTRACT

An important goal of biomedical research is to translate basic research findings into useful medical advances. In the field of neuropharmacology this requires understanding disease mechanisms as well as the effects of drugs and other compounds on neuronal function. Our hope is that this information will result in new or improved treatment for CNS disease. Despite great progress in our understanding of the structure and functions of the CNS, the discovery of new drugs and their clinical development for many CNS disorders has been problematic. As a result, CNS drug discovery and development programs have been subjected to significant cutbacks and eliminations over the last decade. While there has been recent resurgence of interest in CNS targets, these past changes in priority of the pharmaceutical and biotech industries reflect several well-documented realities. CNS drugs in general have higher failure rates than non-CNS drugs, both preclinically and clinically, and in some areas, such as the major neurodegenerative diseases, the clinical failure rate for disease-modifying treatments has been 100%. The development times for CNS drugs are significantly longer for those drugs that are approved, and post-development regulatory review is longer. In this introduction we review some of the reasons for failure, delineating both scientific and technical realities, some unique to the CNS, that have contributed to this. We will focus on major neurodegenerative disorders, which affect millions, attract most of the headlines, and yet have witnessed the fewest successes. We will suggest some changes that, when coupled with the approaches discussed in the rest of this special volume, may improve outcomes in future CNS-targeted drug discovery and development efforts.

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Contents

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1. Introduction

The failure rate for new drugs targeting important central nervous system (CNS) diseases is very high relative to most other areas of drug discovery, a fact reflected in the many pharmaceutical company CNS programs that have been disbanded or significantly reduced (Abbott, 2011; Miller, 2010). This is most apparent in the case of drugs that attempt to alter the course of the disease or condition (disease modifying drugs), and is particularly acute in the area of neurodegenerative diseases (NDDs). In many cases, the drugs that have had demonstrable effects are palliative treatments that have modest effects on disease symptoms and no demonstrable effect on disease progression.

For any disease, it is difficult to discover effective and safe drugs. Discovering and developing a successful drug depends on very detailed knowledge of underlying disease mechanisms and a successful progression from candidate identification to clinical trial design. The pharmaceutical industry (for all the right reasons) is heavily regulated, and it is one of the few industries where, despite the investment of a great deal of capital and time, the majority of efforts result in complete failure. While other industries, such as the aircraft industry, are equally regulated at a certain level, the result of that scrutiny is rarely a completely unusable aircraft, or the irreversible denial of marketing approval for a new airplane. We understand enough about the physics of flight to assure that planes will fly, and an iterative process with regulators makes sure they fly safely. In the discovery and development of new medicines, this is not a certainty: we do not have any *a priori* reason to expect that we can intervene with pharmaceutical agents in any disease, and it is never assured that a drug will be approved for marketing. If the FDA decides that safety concerns, lack of sufficient efficacy or a combination of these factors does not justify approval, there is usually no mechanism to 'fix' the candidate, and the project will likely be considered a failure. Most drugs fail prior to being presented to the FDA for final approval if they clearly do not meet regulatory standards. However, rejection of approval is a reality, as is withdrawal following approval for emergent safety concerns.

Almost miraculously, in many types of disease, such efforts have been very successful, although in very few instances can pharmaceutical treatments be considered cures. Some disease areas, frankly, have proven more tractable than others, and almost all other areas are easier than targeting many types of CNS disease. For example, anti-infective agents target organisms that are foreign invaders in our particular internal ecosystems, presenting almost unlimited opportunity for novel and effective agents to kill pathogens while sparing our own cells. The rapid progress in discovering and developing life-saving medicines in areas such as HIV-AIDS and other viral disease demonstrates that when there is sufficient cooperation between the relevant government agencies, academia and the pharmaceutical/biotech industry, and pressure from patient advocates, progress in such diseases can be very rapid and effective (Fauci, 2003; Hardy, 1994). The same will likely be true with antibiotic resistance and parasitic diseases in the near future, it will just require the political will to do it on a grander scale, and new models for recouping investments for short-term treatments or treatments aimed at third-world patient cohorts. While these types of collaborative efforts have also paid off well in other areas such as cancer and heart disease, thus far they have not led to effective treatments in many of the major CNS disorders. They *have* begun, however, and there is every reason to be optimistic.

In all disease areas, there are several common requirements for designing and implementing a successful effort to discover new treatments. The natural history of the disease or condition *must* be well understood. A potential molecular target has to be identified, and a testable hypothesis must be generated concerning the role of the new molecular target in either the generation or amelioration of the disease state or condition. A model of the disease must be created that is believed to have predictive validity for use in preclinical tests and that involves induction of the disease, or a mechanistically-related disease, in animals or *in vitro*. A directed program must be initiated to generate molecules to test. If a candidate molecule is identified that fulfills a number of preclinical criteria such as dose-dependent efficacy in the model(s), metabolic stability and a sufficient degree of animal safety at multiples of presumed therapeutic doses, a drug candidate may be taken into carefully designed and tightly regulated clinical trials to determine its safety and efficacy. Initially the safety of the drug candidate is tested in healthy human subjects, and eventually in human subjects with the disease. If efficacy is demonstrated that is greater, in the context of the particular disease, than the risks associated with the drug it may be approvable and eventually marketed and made available to patients.

These above steps have been followed in the development of drugs that act on the CNS, but levels of clinical failures are higher than in other therapeutic target areas, most often because of lack of any significant evidence of clinical efficacy. While drugs often fail prior to understanding whether they are efficacious, it is failure for lack of efficacy that is most vexing, expensive and leads to the greatest likelihood of retreat from a disease target. This occurs repeatedly despite seemingly adequate and appropriate preclinical data demonstrating that candidates should work well, and have seemingly adequate clinical safety margins. No one makes the decision to advance a drug into very expensive and time-consuming clinical trials lightly. While there have been some obvious mistakes, usually based on assumptions later proven wrong, the preclinical packages used to propel CNS drugs into the clinic are just as convincing and well-executed as those for any other therapeutic area. Clearly, there is a major disconnect, at least in some CNS subdisciplines. *Post hoc* analyses may point to specific aspects of a clinical trial that may have contributed to the lack of a positive signal, and such analyses are useful and necessary. Failures due to lack of efficacy, however indicate that there may be serious flaws in the hypothesis. As a result, negative results may be critical to understanding how to make successful drugs. Negative results should therefore be published, but often have not been (Hayes and Hunter, 2012; Jones, 2013).